

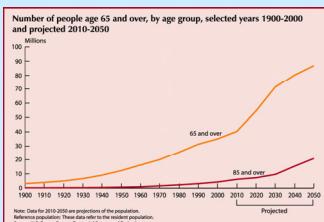
Improving Our Understanding of Susceptibility in the Aging Population to Environmental Exposures

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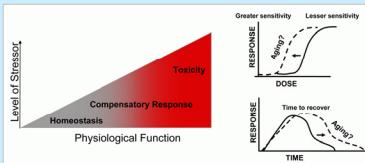
Issue: The American population is aging.

- Older adults may be more susceptible to environmental contaminants.
- Substantial inter-individual differences in susceptibility are anticipated.
- Protecting the aging population is a regulatory, social and economic imperative.



Science questions:

- What critical changes occur with aging in the relationship between environmental exposures and adverse health effects?
- How do aging-related changes in physiology limit the body's ability to maintain homeostasis and respond to injury?
- How does variability between individuals change with age?

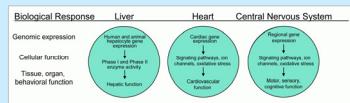


All organisms have the capacity to compensate for the effects of environmental stressors. Frailty and loss of resilience, due to aging processes or changes in health status, may limit those compensatory responses and make it more likely an exposure will result in a toxic response. Frailty may be seen as a shift toward greater sensitivity in the dose-response, and loss of resilience as a lengthening of the time to recover.

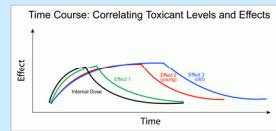
Impact: This research will reduce uncertainties in risk assessment by characterizing aging-related susceptibility, the toxicants and exposures of concern, and the mechanisms underlying susceptibility. This research will also promote accurate estimation of inter-individual differences in susceptibility to insure the safety of the aging American population from environmental exposures.

Approach:

- Phase 1. Descriptive: Toxicant effects on the central nervous system, heart and liver are being determined using a multi-level multi-disciplinary approach.

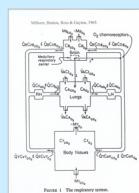


- Phase 2. Mechanistic: Time-course investigations, linking adverse effects with toxicant concentrations in target tissues, will determine pharmacodynamic and pharmacokinetic factors in susceptibility.

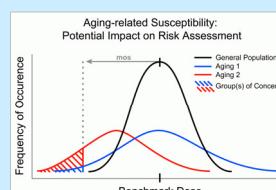


Effect 1 indicates a pharmacokinetic dependence, where the effect diminishes as the toxicant is cleared from the body.
Effect 2 indicates a pharmacodynamic dependence, where the effect lasts long after the toxicant and its metabolites are cleared.
Effect 3 also indicates a pharmacodynamic dependence, but the effect lasts longer in the older subjects.

- Phase 3. Modeling: Quantitative physiological and pharmacokinetic models of aging-related susceptibility will be developed and refined, based on tests of their predictions in experimental and clinical studies.



This classic model depicts relationships between the respiratory system, brain and other organ systems. Modern models have considerably more compartments, but the principle is the same. Organ systems are linked by circulatory, neural and hormonal pathways. The function of each organ, and their interactions, is expressed in differential equations. The model is then used to simulate normal and compromised physiological conditions. Predictions can be tested and the model refined as appropriate. New data (e.g., genomic, proteomic effects) can also be added to improve predictions.



Current approaches to risk assessment identify a "benchmark" dose (e.g., NOEL, LOEL) and then apply a margin of safety (mos) to set a lower exposure that is protective of the general population. The **Aging 1** distribution indicates no change in average sensitivity but an increase in inter-individual variability. (This distribution also indicates the aging population may be less sensitive to some exposures.) The **Aging 2** distribution indicates an increase in both average sensitivity and inter-individual variability. The hatched areas indicate some individuals may be at greater risk than current approaches would anticipate.



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